Rational Design of Triplet Sensitizers for the Transfer of Excited State Photochemistry from UV to Visible

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ABSTRACT: Time Dependent Density Functional Theory (TD-DFT) has been used to assist the design and synthesis of a series thioxanthone triplet sensitizers. Calculated energies of the triplet excited state (E_T) informed both the type and position of auxochromes placed on the thioxanthone core, enabling fine-tuning of the UV-Vis absorptions and associated triplet energies. The calculated results were highly consistent with experimental observation in both the order of the λ_{max} and E_T values. The synthesised compounds were then evaluated for their efficacies as triplet sensitizers in a variety of UV and visible light preparative photochemical reactions. The results of this study exceeded expectations; in particular [2+2] cycloaddition chemistry that had previously been sensitized in the UV was found to undergo cycloaddition at 455 nm (blue) with a 2 to 9-fold increase in productivity (g/h) relative to input power. This study demonstrates the ability of powerful modern computational methods to aid the design of successful and productive triplet sensitized photochemical reactions.

INTRODUCTION

Excited state photochemistry[1] involves the formation of bonds by the reaction of molecules in an electronically excited state. Its purest embodiment occurs without catalysts or reagents by irradiation with UV light, most commonly in the region of 250-400 nm. This 'reagentless' approach to synthesis is highly desirable in an ever more economic and green focused society. Reactions typically occur from either the lowest energy excited singlet (S_1) or triplet (T_1) states, the latter accessed via intersystem crossing (ISC) from the singlet. These 'electronic isomers' of the ground state species can react in exotic ways to give rapid access to complex or highly strained species with favorable properties for drug discovery[2] or further reactivity.[3] Unfortunately the overall efficiency, and hence synthetic utility, of a photochemical reaction is often dependent on the lifetime of these states relative to the rate of chemical reaction, which in turn is determined by the physical properties of the compound. Therefore, many interesting photochemical reactions may remain of academic curiosity due to poor yields and low-productivities. Whilst the short-lived S_1 state is inherently difficult to control, the much longer lifetime of the T_1 state can be exploited to significantly enhance the overall quantum efficiency of a reaction.

Since the early 1960s[4] it has been understood that photosensitizers can enable population of the T_1 excited state of a substrate by energy transfer even though the substrate does not absorb at the sensitizer absorbing wavelength (Figure 1A). As a result a number of photochemical reactions have been enabled by sensitization when direct irradiation has been ineffective.[5] The ideal triplet sensitizer has a strong extinction coefficient to allow for efficient light absorption at low concentrations, a relatively small S_1-T_1 energy difference for irradiation at the longest wavelength, ISC close to unity for maximum quantum efficiency and a long lived T_1 state for efficient energy transfer to a ground state species. All these features can circumvent the most common causes for a low productivity in a photochemical reaction. Furthermore, where the singlet and triplet manifolds have different reaction outcomes it is possible to switch between S_1 and T_1 chemistry by addition of a sensitizer.[6]

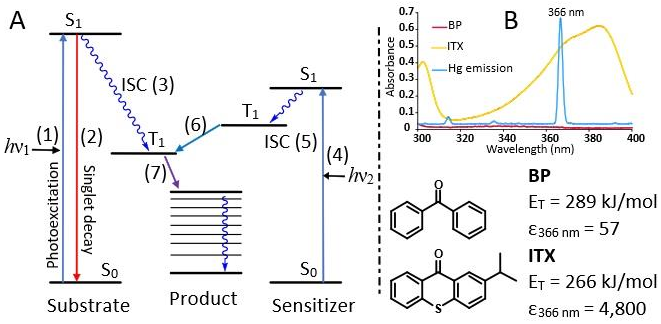


Figure 1. (A) Simplified Jablonski diagram of a triplet mediated photochemical reaction: (1) Direct excitation of substrate to S_1; (2) Singlet decay by radiative and non-radiative processes; (3) ISC to reactive T_1; (4) Photoexcitation of sensitizer; (5) Rapid ISC to T_1; (6) Triplet energy transfer to substrate; (7) Chemical reaction and relaxation to ground state. (B) UV absorption of BP and ITX at 1×10^{-4} M, overlaid with UVA emission from medium pressure Hg lamp.

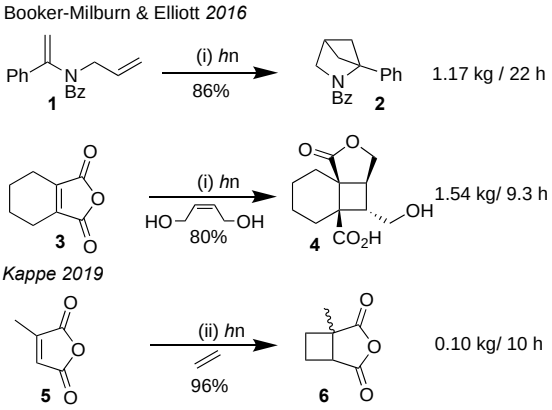
In addition to an energy transfer pathway, sensitizers have also allowed for efficient scale-up of photo-initiated processes by alternative methods.[7] For example, in recent years there has been explosive growth in the development of photoredox catalysis,[8] i.e. organic or organometallic catalysts that upon photoexcitation act as powerful one-electron oxidants or reductants in a

variety of bond forming processes. Modification of a ligand on a transition metal complex[9] or substituents on an organic dye[10] allows the redox potential to be fine-tuned to match that of a substrate. Within this recent work it has been found that some of the organometallic photoredox catalysts can alternatively function as classic triplet sensitizers in, for example [2+2] photocycloadditions.[11] However, the possibility that transition metal photocatalysts can react via either electron or energy transfer can make determination of the mode of activation difficult as highlighted in a recent study on eniminium [2+2] cycloaddition using laser flash photolysis.[12]

Herein we report the rational design of a family of *triplet sensitizers* for chemical synthesis[13] that share a common chromophore, but individually cover a range of triplet energies. From our experience of photochemical synthesis in the UV, we were inspired to design a range of organic sensitizers that would span the 350-450 nm region.

A key goal of the present study was to see if it was possible to move useful UV chemistry into the visible (≥ 400 nm) with similar or better productivities to match readily available high intensity LED light sources. It should be noted that use of sensitizers can result in practical issues, especially if energy transfer is inefficient or the sensitizer has a low extinction coefficient (ε). In these instances high sensitizer concentrations/equivalents are required (e.g. acetophenone & acetone), often resulting in degradation, purification and separation issues. With this in mind we considered the design of highly absorbing sensitizers that could be used in low molar equivalences and be stable to high UV/Vis powers (≥ 500W). Traditionally, sensitizer screens involve a range of chromophores with different triplet energies, but very different absorption characteristics (cf. BP and ITX, Figure 1B). A sensitizer series based around single chromophore is therefore highly desirable for consistency and reliability.

Scheme 1. Scale-up of [2+2] photocycloadditions using thioxanthone sensitization.



In 2016 as part of a campaign to enable the scale-up of UV photochemistry using flow-reactors we designed a parallel tube flow reactor (PTFR)[14] which displayed productivities of between 1-8 kg/day for a range of photochemical reactions in the UV (Scheme 1). The large-scale examples in Scheme 1 required a triplet sensitizer to enable a productivity increase to multi-kg/day quantities. Of a number of sensitizers screened, isopropylthioxanthone (ITX) was demonstrably superior in terms of productivity at exceptionally low loadings (1%). The isopropyl derivative proved to be more soluble than the parent thioxanthone, making bulk purification by trituration easier. The high extinction coefficient of ITX (Figure 1B) is important for its excellent sensitization properties at the 1% loadings used, and remarkably we found no sensitizer degradation was observed despite the very powerful 3 kW Hg-UV lamp employed.

In 2019 Kappe[15] reported a study of maleimide and maleic anhydride [2+2] cycloadditions (UVA) using a variety of known sensitizers chosen for their matching triplet energies. They also observed that thioxanthone proved to be a superior sensitizer where the substrate triplet energy was a suitable match. In the visible region, Bach[16] has shown that thioxanthone can be used as a sensitizer by irradiation at the tail of the absorption using 420 nm light. Jockush and Sivaguru[17] have shown that 2,2'-bromo thioxanthone induces a moderate (~15nm) bathochromic shift enabling sensitized cycloadditions with near UV light (395-405nm). However, photolabile halo derivatives (Cl, Br, I) can be problematic due to the potential of photodehalogenation.[18] A further advantage of thioxanthone over other common sensitizers, such as BP is the nature of the reactive triplet state. For TX this is (π, π^*) whilst for BP it is (n, π^*) making TX less likely to take part in competing H-atom abstractions which are well documented for BP and derivatives.[19]

RESULTS and DISCUSSION

DFT Informed Sensitizer Design. It was our aim to induce predictable shifts in absorbance by substituting thioxanthone with a range of auxochromes that electronically modify the UV/Vis absorption of a chromophore. Rather than embark on a time consuming hit-and-miss synthetic approach, we opted to use time-dependent density functional theory (TD-DFT) to calculate the triplet energies for a range of auxochrome substituted thioxanthone derivatives. This would enable the selection of potential sensitizer candidates to be made before synthesis. In terms of substituents we chose a balance between those that are known auxochromes and would likely be photochemically robust. Based on prior experience with substituted benzophenones and acetophenones we narrowed down the auxochrome choice to fluoro- and methoxy-substituents.

Initial TD-DFT calculations of thioxanthone derivatives bearing these two auxochromes were highly informative in predicting a sensitizer series spanning a broad range of triplet energies. Once a range of nine candidates were selected from these computational studies, they were then synthesized using an Ullman coupling/Friedel Crafts approach (see SI).

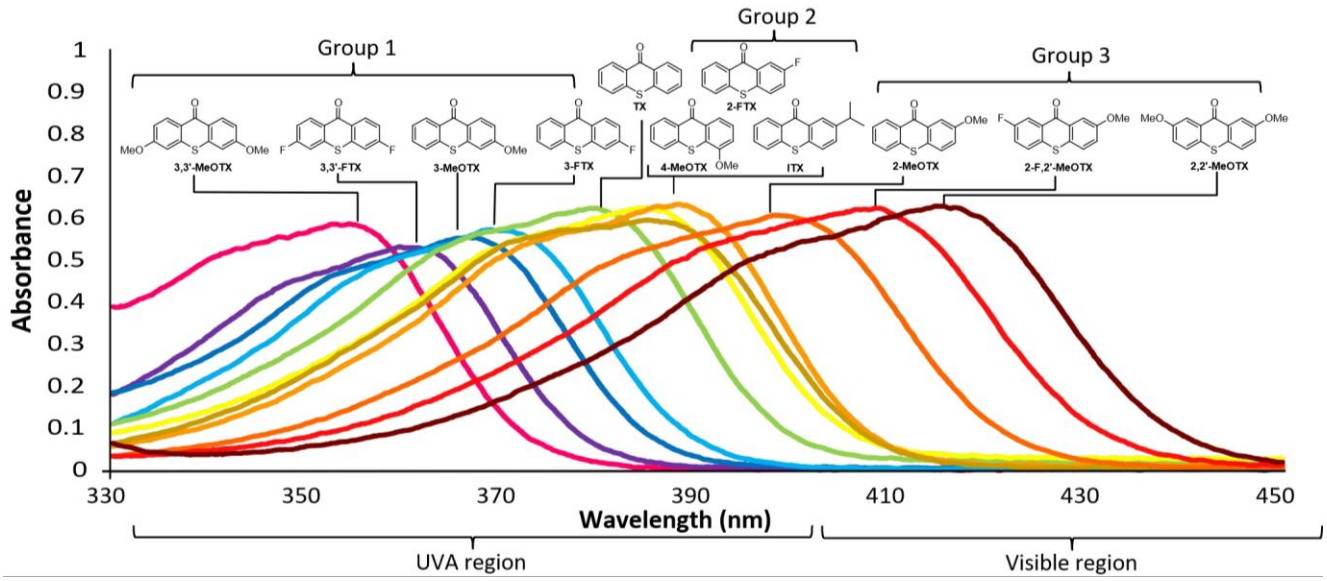


Figure 2. UV-Vis absorption spectra for the synthesized thioxanthone sensitizer series including the parent commercially available thioxanthone and 2-isopropyl thioxanthone. All were run at a concentration of 1×10^{-4} M in acetonitrile.

Photophysical Characterisation. The UV-Vis absorption of the nine synthesized thioxanthone derivatives (plus TX and ITX) are represented in Figure 2 as a composite spectrum for comparison. The placement of these auxochromes has the desired effect of shifting the UV-Vis absorption relative to the parent thioxanthone core. In the UV-Vis spectra, substituents in the 2-position induce a bathochromic shift whilst 3-substituents induce a hypsochromic shift compared to the parent thioxanthone, in excellent agreement with DFT. The effect is more pronounced for the MeO derivatives (compared to F) and the effect is additive. The sensitizer absorption energies can be split into three distinct groups. Absorbing at shorter wavelengths, and hence higher energies than the parent thioxanthone, are the series of 3-substituted thioxanthones (Group 1). Within this group a clear energy order is apparent with 3,3'-MeOTX > 3,3'-FTX > 3-MeOTX > 3-FTX. Absorbing at slightly longer wavelength, and hence lower energy than TX are the 2-FTX and 2-iPrTX derivatives along with 4-MeOTX (Group 2). These absorbances are clustered close together but an expansion of the weak tail end at longer wavelengths suggests ITX > 2-FTX ≥ 4-MeOTX. The absorbances of the Group 2 series, along with TX begin to overlap with the visible region of the spectrum above 400 nm. Absorbing at significantly longer wavelengths are the series of 2-MeO derivatives with a clear energy order 2-MeOTX > 2-F,2'-MeOTX > 2,2'-MeOTX (Group 3). This moves the lowest energy absorption bands well into the visible region and is expected to enhance their efficiency as visible light active triplet sensitizers with readily available and powerful LED sources (e.g. 36 W at 455 nm).

Table 1. Calculated and measured photophysical parameters for substituted thioxanthone derivatives

Entry	TX	λ_{max} (nm)[a]	$E_{T\ (Calc.)}$[b] (kJ/mol)	$E_{T\ (Calc.)}$[c] (kJ/mol)	$E_{T\ (Meas.)}$[d] (kJ/mol)	τ_S[g]	τ_T[h]	Φ_{ISC}[i]
1	3,3'-MeOTX	354	292	289	298 [e]	10 ± 3 ps	862 ± 40 ns	0.93
2	3,3'-FTX	362	290	285	289 [e]	10.5 ± 1.8 ps	456 ± 25 ns	0.92
3	3-MeOTX	367	284	279	283 [e]	31 ± 4 ps	867 ± 50 ns	>0.9
4	3-FTX	370	282	277	282 [e]	21 ± 3 ps	520 ± 25 ns	0.83
5	TX (R/R'=H)	380	274	268	274 [e]	70 ps[20]	760 ± 30 ns	0.76[17]
6	ITX (R'=H, R = 2-^{i}Pr)	385	270	263	266 [e]	220 ± 8 ps	880 ± 50 ns	0.86
7	2-FTX	388	263	257	261 [e]	270 ± 10 ps	585 ± 20 ns	0.81
8	4-MeOTX	385	267	260	263 [e]	1.9 ± 0.4 ns	1.8 ± 0.3 µs	0.70
9	2-MeOTX	399	252	245	242 [f]	3.3 ± 0.2 ns	1.7 ± 0.6 µs	0.83
10	2-F,2'-MeOTX	408	242	235	235 [f]	9.1 ± 0.7 ns	1.2 ± 0.2 µs	0.62
11	2,2'-MeOTX	415	235	227	231 [f]	6.2 ± 0.5 ns	863 ± 60 ns	0.66

[a]Longest wavelength absorption maximum (MeCN); [b]Calculated E_T, no solvent model, B3LYP 6-31G (d,p); [c]Calculated E_T, no solvent model, B3LYP 6-31+G (d,p); [d]Measured E_T (Phosphorescence, [e]MCH glass, 77 K; [f] 2-MeTHF glass, 77 K); [g]Singlet lifetime measured with TRIR, CD_3CN; [h]Triplet lifetime measured with TRIR, CD_3CN; [i]ISC quantum yield calculated from bleach recovery kinetics

The TD-DFT calculated triplet energies for the thioxanthone derivatives are summarized in Table 1 along with the corresponding λ_{max} and E_T as measured by phosphorescence emission spectroscopy. Gratifyingly the TD-DFT calculated triplet energies corresponded well with the order of the observed absorption λ_{max} and measured E_T values. The three lowest energy (group 3) derivatives displayed overlapping fluorescence and phosphorescence in MCH at 77 K which hampered the estimation of the triplet energy. The analysis of the emission spectra of these compounds in 2-MeTHF at 77 K more readily allowed estimation of the triplet energy (Table 1, entries 9-11). The thioxanthone derivatives span a remarkably wide range of triplet energies from approximately 230 to 290 kJ/mol. As a point of reference, benzophenone has a triplet energy of 289 kJ/mol,[21] thioxanthone 274 kJ/mol[22] and $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ is 255 kJ/mol.[23]

Also shown in Table 1 are the singlet and triplet lifetimes, as measured using ps and ns time-resolved infrared spectroscopy (TRIR) as this structurally sensitive technique allows characterisation and dynamics of both the singlet and triplet species, together with an estimation of the triplet quantum yield in one convenient measurement at room temperature. These measurements showed a large variation in singlet state lifetime with the different thioxanthone derivatives. The higher energy derivatives with substituents in the 3-position have much shorter singlet state lifetimes before undergoing ISC to the triplet state. These singlet lifetimes are approximately 1000× shorter lived than the lowest energy derivatives (entries 8-11).

Consistent with previous computational studies of thioxanthone,[24] DFT calculations predicted the lowest excited singlet state (S_1) was of ππ* character and S_2 was nπ* in polar solvents (MeCN). The T_1 states were calculated to be of ππ* character, regardless of solvent polarity. There was a strong correlation between the measured singlet state lifetime and the S_2(nπ*)- S_1(ππ*) energy difference (See SI). The smaller the energy difference, the faster the rate of ISC to the triplet state. This could possibly be due to increased involvement of the nπ* state, when it is sufficiently close in energy, allowing faster ISC to the triplet states due to El-Sayed's rule.[25] This has previously been observed in the case of 1-azathioxanthones which were investigated as antenna chromophores in lanthanide (III) based dyes.[26] Triplet quantum yields (Φ_{ISC}) were estimated using bleach recovery kinetics. These were generally between 80 – 90%, but the two lowest energy derivatives, along with 4-MeOTX, were measured at just 60 - 70%.

Sensitizer Evaluation in Alkene Isomerisation. We first assessed the performance of these sensitizers in the simple isomerization of *trans*-alkenes to photostationary *cis*/*trans* mixtures (Figure 3). Using the pure *trans*-isomers of both β-Me styrene ($E_{T(E)}$ = 249 kJmol^{-1}, $E_{T(Z)}$ = 275 kJmol^{-1})[21] and methyl cinnamate (E_T = 229 kJmol^{-1})[21] each of the 10 sensitizers were investigated in turn for their ability to effect a photostationary *cis*/*trans* isomer mixture. To allow rapid screening of the whole sensitizer series with minimal material usage, 0.5 ml samples (0.2 M, 5% sensitizer) in deuterated acetonitrile were irradiated in NMR tubes placed next to a 9 W PL-S low pressure UVA lamp. Multiple samples could be irradiated at once and the reaction was monitored by periodic ^{1}H-NMR analysis. Pleasingly, for all 10-sensitizers isomerization to a photostationary state was observed within a similar reaction time (30-45 mins), implying equally efficient overall energy transfer rates. These results immediately demonstrated that the full range of thioxanthone sensitizers can all act as effective sensitizers if the triplet energy is sufficiently high.

Higher energy Group 1 sensitizers gave essentially 1:1 isomerized mixtures in both cases. Slight enrichment in the *cis*-isomer was observed for the medium energy Group 2. Significant enrichment in the *cis*-isomer was observed for the lower energy Group 3 which reached a maximum of 5:1 for β-Me styrene and 2:1 for methyl cinnamate when 2-F,2'-MeOTX was used. Although initially a surprise, this is a known trend observed by others and can be attributed to selective sensitization of the *trans*-isomer with lower energy sensitizers.[27] The subsequent drop in *cis*/*trans* ratio for the lowest energy sensitizer was also noted in the earliest studies and the unusual behaviour observed for low energy triplet sensitizers has been attributed to non-vertical triplet energy transfer.[28] Recently there has been renewed interest in the use of organic/organometallic sensitizers for enrichment of *cis*-styrenes by selective isomerization of *trans*.[29]

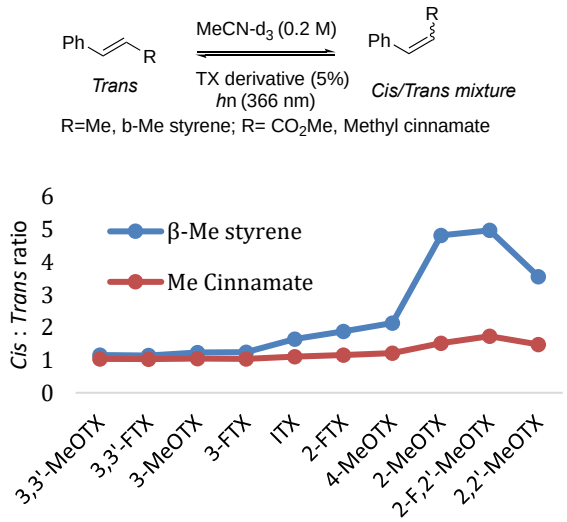


Figure 3. Photostationary *cis/trans* ratios of β-Me styrene and methyl cinnamate with the full range of substituted TX sensitizers at 366 nm (low-pressure UVA lamp).

Sensitizer Evaluation in Preparative Photochemistry. To investigate the effectiveness of the sensitizer set on a preparative scale, reactions were screened for the intra- and intermolecular [2+2] cycloadditions shown in Figure 4 using a 125 W medium pressure Hg-lamp and a 150 ml immersion well batch reactor. Despite the large predicted triplet energy range, the intramolecular cross [2+2] (Reaction A) showed only moderate variation of productivity across the sensitizer range. This was maintained, even in the case of lowest energy derivative (2,2'-MeOTX). The final yields, as determined by quantitative NMR all exceeded 90% at full conversion.

The intermolecular [2+2] of THPA and propargyl alcohol (Reaction B)[30] also proceeded with a similar productivity of 22-26 mmol/h with the first six highest energy sensitizers. The productivity then drops off sharply to 8 mmol/h with 4-MeOTX. This is presumably when the triplet energy of the sensitizer falls below that of THPA. At full conversion the

[2+2] yields all reached around 75%, which is typical for this reaction.

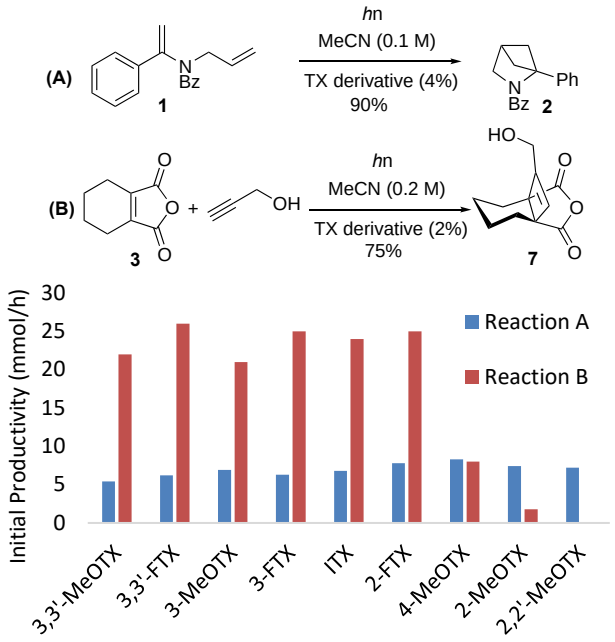


Figure 4. Initial productivities of intra- and intermolecular [2+2] cycloadditions (A) and (B) with a 150 ml immersion well batch reactor and 125 W Hg lamp

Reactions (A) and (B) are both well-studied and reliable triplet sensitized photochemical reactions. To further test the synthetic use of the sensitizer set, a reaction was investigated which is more sensitive to variations in reaction conditions (Figure 5). Reaction (C) is a novel cross [2+2] / retro-Mannich sequence giving γ-amino acid derivative **10**.[31] In all cases the initial productivity was around 3 mmol/h but there was a large variation in yield across the sensitizer series, with the higher energy sensitizers giving the greatest yields. 3,3'-MeOTX stands out as giving the highest isolated yield of 66%. Conversely, the lowest energy sensitizer (2,2'-MeOTX) resulted in almost full degradation of the reaction mixture within a short period of time. It is possible that the lower energy sensitizers could be undergoing electron transfer from the electron rich enamine or amine intermediate.[32]

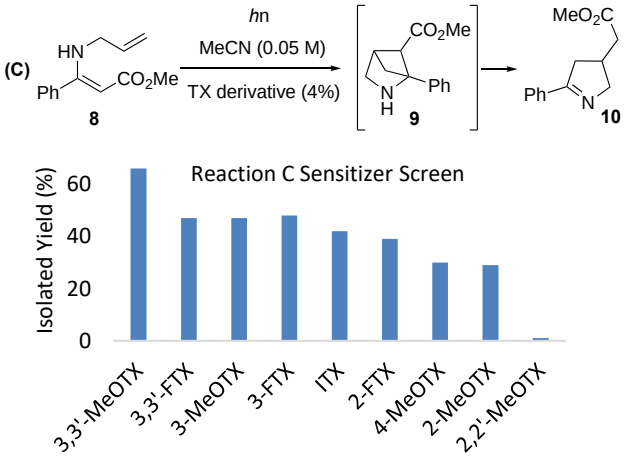


Figure 5. Isolated yields of [2+2] / retro-Mannich product **10**

The above examples were optimized on a preparative scale with a 150 ml batch reactor due to the ready availability of the starting materials. In cases where the photochemical precursor synthesis is more difficult, it was prudent to screen irradiation conditions on a small scale to save material and prevent unnecessary wastage of the sensitizer. The NMR technique described above was used for optimisation of the cycloaddition of amino acrylate **11** (Reaction D), which had previously been carried out under acetophenone sensitisation.[33] Nearly all the TX sensitizers proved to be very effective in the conversion of enamide **11** (Figure 6). However, unlike the related styrene reaction (Reaction A), the lowest energy sensitizers became ineffective (E_T < 2-FTX).

The unoptimized cross [2+2] of the enamide **13** to **14** represented a more complex multi-chromophore system and proved to be consistently low yielding, requiring long reaction times, with both benzophenone and ITX sensitizers (Reaction E, Table 2, Entry 1&2). Using the NMR tube irradiation method we were able to screen the full sensitizer series in deuterated acetonitrile, using just 0.5 mmol of enamide **13**. It was found that there was a large variation in yield and productivity across the sensitizer range. The maximum yield was limited to just above 50% and obtained with the highest energy sensitizer 3,3'-MeOTX. Moving down in triplet energy it can be seen that the yields and productivity drop off rapidly (Figure 6).

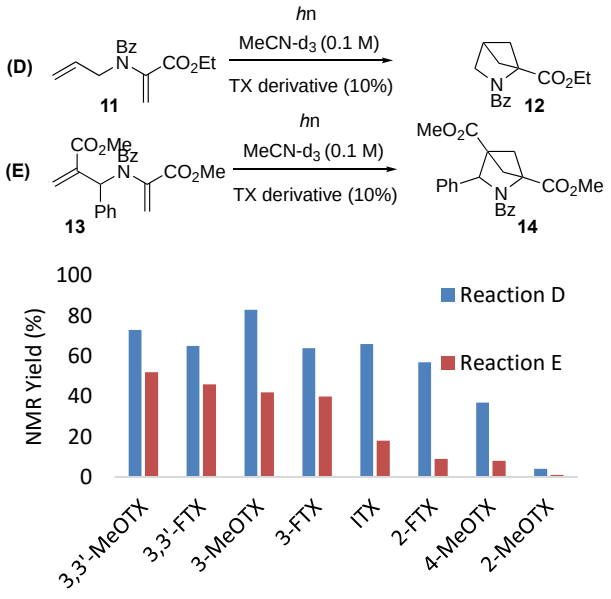
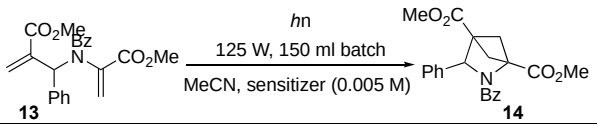


Figure 6. 0.5 ml NMR tube sensitizer screen (366 nm) for rapid optimization of reactions (D) and (E). Yield determined by adiponitrile internal standard after 15 min (D) and 30 min (E)

The value of this rapid NMR method can be seen in the translation of the screening results to the scale-up of Reaction E (Table 2). Using the conventional benzophenone sensitizer gave just over 1g of **14** after 9h irradiation. Conversely using the 3,3'-MeOTX sensitizer identified from above we were able to prepare 5.8g of product in 7 h and in the *same yield* as identified from screening. This result is of significance since the DFT calculations indicate both benzophenone and 3,3'-MeOTX share very similar triplet energies, yet 3,3'-MeOTX is a far superior sensitizer. Both 3-FTX and ITX showed the

same drop off in yield and productivity as observed in the NMR screening reactions.

Table 2. Preparative scale reactions using 125 W medium-pressure Hg-lamp in a 150 ml batch reactor



Entry	Sensitizer	Conc. (M)	Time (h)	Yield	Mass (g)
1	BP	0.05	9	46	1.3
2	ITX	0.05	12	38	1.1
3	3-FTX	0.05	5	51	1.45
4	3,3'-MeOTX	0.1	3	56	3.2
5	3,3'-MeOTX	0.2	7	51	5.8

Development of a Visible Light Reactor for Preparative Photochemistry. We then turned our attention to the Group 3 sensitizers, which due to their longer wavelengths of absorption (> 400 nm) should be capable of facilitating triplet state photochemistry in the visible region. Our aim was to enable preparative scale photochemistry with low sensitizer loadings (≤ 1 mol%) using readily available powerful visible light LED sources. Reported visible light mediated photoredox reactions are often driven by a 40 W Kessil lamp or a flexible LED strip placed side-on and a few centimetres away from a vial containing the reaction solution. The overall light capture is poor and as a result the reactions are often left on overnight to drive a successful reaction to completion (Figure 7A). The side-on method of irradiation is necessary since the vials are stirred over a magnetic stirrer and there is no room below for a commercial light source. A successful (4×1.1 W) device for addressing this problem was recently described by McMillan *et al*[34] for optimizing photoredox chemistry and has been commercialised and utilised in a number of labs worldwide.

For our present triplet sensitizer focussed chemistry we required significantly higher-powered devices to take productivities from mg/h to multi-grams/h. We have recently shown that excited state photochemistry can be scaled-up predictably with increasing lamp power since the reactions are often photon limited and have a linear relationship with photon-flux.[35]

Our past experience with the design of UV flow reactors for excited state photochemistry[14,35,36] demonstrated that much higher productivity levels (≥ kg per day) could be achieved if careful attention was paid to light capture by the photosylate. We therefore sought to engineer a visible light system for sensitised photochemistry at input powers of at least 30 W, which could exploit the high-power density of modern visible LED's in conjunction with readily available lab components such as hotplate stirrer (Figure 7B). To achieve this, we designed a high-intensity blue light reactor system based around *chip-on-board* (COB) LEDs with peak emissions at 455 nm. As these COBs have an output of 36 W from a circular area of only 22 mm diameter, they are ideal for delivering a high photon flux to a standard round bottom flask (50-100 ml). Figures 7C and D show a 36 W COB attached to a standard magnetic stirrer in close proximity to a round bottom flask. The magnetic stirrer surface acts as a heat sink and a small fan prevents hot air stagnating around the flask.

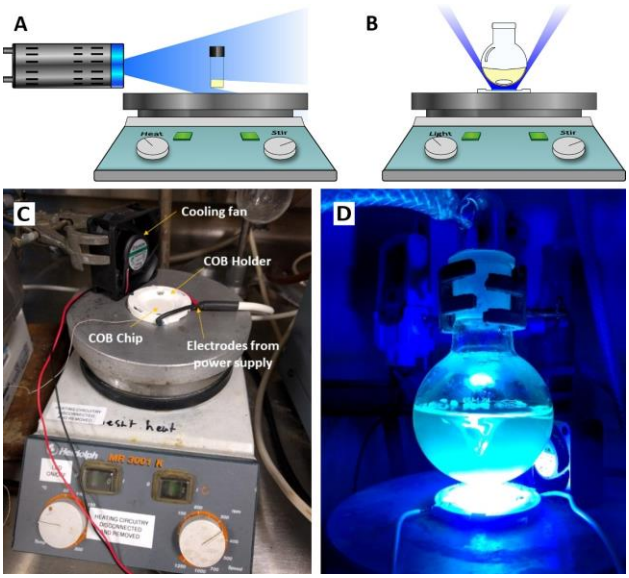


Figure 7. (A) Inefficient side-on irradiation with external lamp over magnetic stirrer. (B) Novel integrated COB LED and magnetic stirrer for maximum light capture. (C) Prototype 455 nm 36 W COB reactor system. (D) Trial reaction, demonstrating irradiation of a stirred vessel

Scale-up of Triplet Sensitized Photochemistry with Visible Light. Simple alkene [2+2] cycloadditions cannot be achieved by direct UV irradiation as alkene absorption is normally ≤ 200 nm. Conjugated alkenes such as styrene undergo sensitized photochemistry from an easily accessible triplet. The cinnamyl alcohol derived diene **15** was chosen as a test substrate. Yoon[11a] was the first to demonstrate that this substrate underwent [2+2] cycloaddition to the cyclobutene ether **16** in 80% yield after irradiation with white light (23 W) for 28 h with 1 mol% $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ catalyst. We repeated this useful reaction using 2,2'-MeOTX (1 mol%) as sensitizer in a MeCN solution of **15** (0.5 M) with the 455 nm 36 W COB reactor. Remarkably, after just 3 h irradiation (Table 3, Entry 1) the reaction was complete allowing for the isolation of 1.5g (89%) of **16** (0.5 g/h). The aza analogue **17**[37] performed even better, providing a high yield (87%) of the bicyclic amine **18** with a productivity of 1.43 g/h.

Interestingly, Oderinde *et al* recently reported[37b] that the cycloaddition of **17** proceeded using 450 nm irradiation (34 W) and 5 mole % $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ to give 152 mg of **18** in over 24 h. As a like for like comparison this demonstrates that, in conjunction with the 36 W COB reactor, 2,2'-MeOTX at just 1 mol% loading is over *225 times* more productive (g/h). As this is the most commonly[11] used Iridium based sensitizer for cycloaddition, 2,2'-MeOTX and related sensitizers may find use as convenient and low cost alternatives.

The intramolecular cross [2+2] cycloaddition of amino styrenes has previously been carried out by us in the UV at high concentrations (0.1-0.4 M) with a 400 W Hg lamp, ITX sensitizer in a Pyrex immersion well batch reactor.[3a] In this work we first chose to study these reactions with the visible light absorbing Group 3 sensitizers using the blue 36 W COB and enamide **1**. As can be seen from Figure 8 all three sensitizers (1 mol %) were highly effective at 455 nm. In particular 2,2'-MeOTX gave complete conversion to **2** in under 2 h (0.5 M), presumably due to the more optimal overlap of the absorption bands with the emission of the COB at 455 nm.

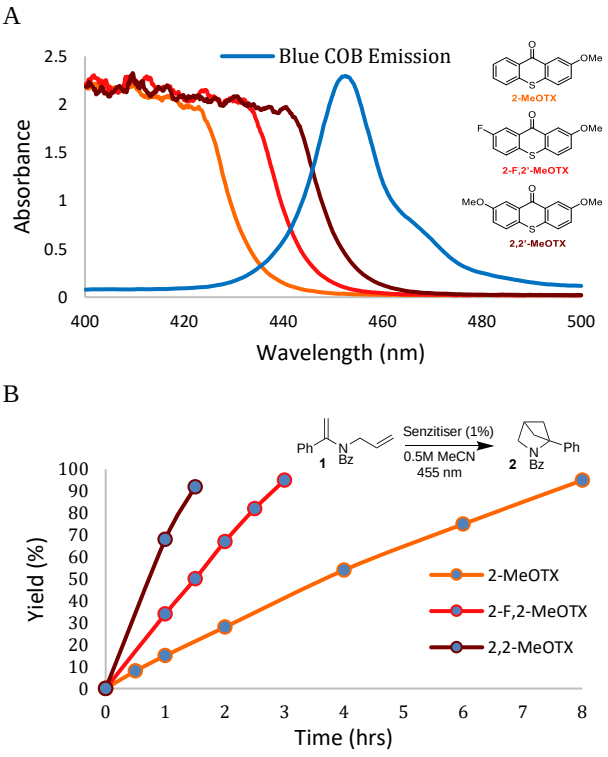


Figure 8. A comparison of (**A**) UV-Vis absorption spectra and (**B**) reaction profiles for 3-different visible light sensitizers at 455 nm with the blue COB LED reactor.

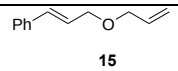
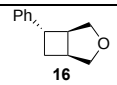
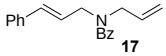
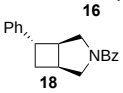
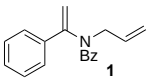
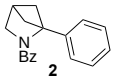
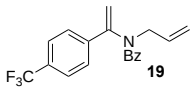
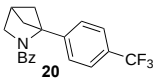
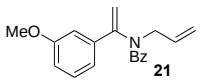
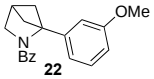
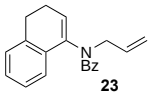
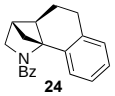
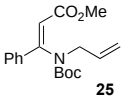
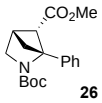
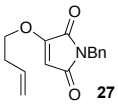
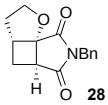
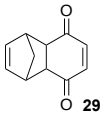
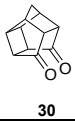
We then undertook a preparative study of 5 different enamides using the absorption matched 2,2'-MeOTX/COB system (Table 3, entries 3-7). In all cases this proved to be a remarkably efficient combination, with their productivities exceeding all expectations e.g. up to 6 g/h of **20**. To put this in context, for entries 4 and 7, a single 36 W COB system approached the productivity of the much larger and more powerful 400 W Hg lamp. For this reaction class the visible light COB /2,2'-MeOTX combination was 6 - 9× more energy efficient than the ITX/Hg lamp reaction. Unlike the NH cinnamate **8** the Boc protected derivative **25** undergoes cycloaddition without degradation with the low energy sensitizer 2,2'-MeOTX. Compared to the UV conditions this reaction also showed a 9× increase in energy efficiency when carried out with 2,2'-MeOTX and the blue COB reactor.

Moving away from styrene chromophores we studied the performance of the alkoxy-maleimide **27** which proved to be a productive cycloaddition using a 125 W Hg UV lamp when irradiated directly (no sensitizer). Pleasingly, carrying out the same reaction at 455nm with 2,2'-MeOTX gave the product **28** but with more than twice the energy efficiency (productivity per W). Finally, the well-studied Cookson's dione[38] **30** was produced in high yield at 455 nm with 2,2'-MeOTX and with more than twice the productivity per W compared to the customary direct irradiation with UV. As with all the other examples the reaction was repeated with 455 nm in the absence of sensitizer and surprisingly was observed to proceed with identical productivity (6 g/h). This interesting observation has not been previously reported in the literature and close inspection of the UV-Vis spectra of the pale yellow starting dione revealed a weak, but significant absorption tail overlapping with the output of the 455 nm COB. This move to the visible should prove to be a useful observation for a variety of Cookson's dione type cycloadditions[39] which have previously thought to have been restricted to the UV.

CONCLUSION

This study has demonstrated that modern DFT methods can be used to inform the design (pre-synthesis) of a family of thioxanthone sensitizers that span the UV-Vis region (300-450nm). Based on this design 9 previously untested sensitizers were synthesised and their DFT calculated triplet energies (E_T) found to be in excellent agreement with those measured by phosphoresce. A rapid NMR screening method was developed to test the efficacy of the entire sensitizer range and proved very effective in optimizing conditions for the scale-up of [2+2] cycloadditions. A new 36 W COB reactor system was developed for the optimal visible light (455 nm) irradiation of stirred vessels. The lower triplet energy sensitizers were found to perform as outstanding sensitizers at 455 nm for a variety of photocycloaddition reactions previously attempted in the UV. For example, on a W per W basis the 2,2'-MeOTX sensitizer, at just 1% loading, proved to be 2-9 times more productive than the corresponding UV reactions. Furthermore, for the same power input 2,2'-MeOTX outperformed Iridium based visible light sensitization of [2+2] cycloadditions by over 200 times (g/h). These outstanding results pave the way for the rational computational design of low-cost, non-metal based organic sensitizers. This should enable the transfer of a range of useful preparative photochemical reactions from the UV to the visible region of the spectra, where modern, compact, powerful and efficient LED based sources are available.

Table 3. Visible light 2,2'-MeOTX triplet sensitized [2+2] cycloadditions of alkenes with a 36 W 455 nm COB and comparison to ITX sensitized process in UV

				36 W Blue / 2,2'-MeOTX		UV/ ITX	
#	Starting Material	Product	Time h	Yield % (g)	Productivity g/h (mg/h/W)	Productivity g/h (mg/h/W)	Efficiency Blue vs. UV
1	 15	 16	3	89 (1.54)	0.51 (14.2)	0.85 (6.8)	2.1×
2	 17	 18	5	87 (7.13)	1.43 (39.7)	1.15 (9.2)	4.3×
3	 1	 2	3	83 (6.58)	2.19 (60.8)	3.89 (9.7)	6.3×
4	 19	 20	1.5	91 (9.05)	6.03 (167.5)	7.11 (17.8)	9.4×
5	 21	 22	3.5	88 (7.78)	2.22 (61.7)	3.51 (8.8)	7.0×
6	 23	 24	6	68 (5.87)	0.98 (27.2)	1.98 (5.0)	5.5×
7	 25	 26	3.75	84 (7.98)	2.13 (59.2)	2.63 (6.6)	9.0×
8	 27	 28	1.5	92 (2.38)	1.59 (44.1)	2.38 (19.0)[a]	2.3×
9	 29	 30	0.4	92 (2.41)	6.0 (166.7)	9.52 (76.2)[a]	2.2×

[a]UV results (125W) using no sensitizer

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/xxxxxxx

Experimental and spectral details for all new compounds and all reactions reported (PDF)

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ACKNOWLEDGMENT

We thank the EPSRC for funding (EP/P013341/1; EP/L003325/1). We thank Dr. Hazel Sparkes for X-ray crystallography of compounds **25** and **26** and Dr Xue Zhong Sun for helpful discussions and assistance with the TRIR measurements.

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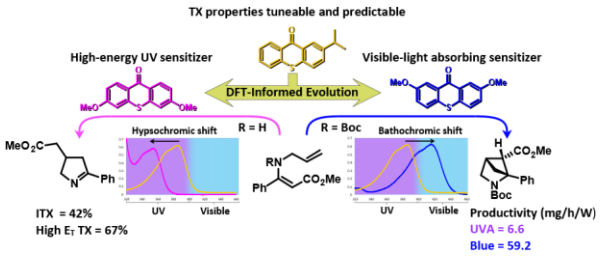
TX properties tuneable and predictable
High-energy UV sensitizer
Visible-light absorbing sensitizer
DFT-Informed Evolution
Hypsochromic shift
R = H
R = Boc
Bathochromic shift
UV
Visible
UV
Visible
ITX = 42%
High E_T TX = 67%
Productivity (mg/h/W)
UVA = 6.6
Blue = 59.2